Medical Staff Conference

Hyperkalemia

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143

DR SMITH:* *Potassium is the main cation of intracellular fluid. Its concentrations are carefully regulated through mechanisms still somewhat obscure. Only 2% of potassium is in extracellular fluid. An acute shift of only another 2% into this compartment might well be fatal. In effect, therefore, we live in hazard "below" a huge reservoir of potassium, a modest spillage of which would be incompatible with life. As a consequence, hyperkalemia is not infrequently a medical emergency. In this Medical Staff Conference Drs Miriam Alvo and David G. Warnock will review for us some of the basic mechanisms that maintain potassium homeostasis and the available means of treating hyperkalemia when those mechanisms fail.*

DRS ALVO AND WARNOCK:†‡ Remarkable strides have been made in our understanding of potassium homeostasis. The most exciting advances concern the mechanisms by which the normal intracellular-to-extracellular ratio of potassium is maintained and defended. Hyperkalemia is singled out in this review because it is one of the most lethal electrolyte disorders when improperly managed in the acute care hospital setting. Newer insights into potassium homeostasis have provided a clearer perspective on the causes of hyperkalemia and have placed the therapeutic approaches on a much firmer basis.

The purpose of this review is to integrate this new information into the clinical approach to hyperkalemia. The normal distribution of total body potassium stores will be considered first, followed by a description of how the distribution of potassium stores is regulated. The clinical syndromes of hyperkalemia will be described next. The clinical approach to hyperkalemia will be organized around those factors that acutely regulate the distribution of potassium stores and the factors that affect potassium excretion by the kidney in chronic conditions.

Total Body Potassium Stores

Extracellular potassium concentration is strictly regulated and depends on the interaction between potassium intake, internal potassium distribution and excretion of potassium. Total body potassium is approximately 50 to 55 mEq per kg of body weight (3,500 mEq in a 70-kg person). Intracellular potassium concentrations are 30 times greater than extracellular potassium concentrations and potassium constitutes the main intracellular cation. The maintenance of a high intracellular potassium concentration and a low intracellular sodium concentration is accomplished by the sodium pump (Na^+ K^+ ATPase) located in the cellular membrane. Only 2% of total body potassium (70 mEq) is located in the extracellular compartment; therefore, a relatively small shift of intracellular potassium can result in a significant change in extracellular potassium concentration.

Dietary potassium intake is 70 to 100 mEq per day, 90% of which is absorbed in the upper gastrointestinal tract. Normally, 90% of the absorbed dietary potassium is excreted by the kidneys and 10% is secreted by the colon. Gastrointestinal losses can increase greatly if renal secretion of potassium is impaired.

Regulation of Extrarenal Potassium Homeostasis

The body's immediate response to a potassium load is mainly regulated by extrarenal tissues; 80% of a potassium load is rapidly translocated into nonrenal cells (mainly muscle and liver cells). The renal response is much slower; 50% of the potassium load will be excreted in the urine during the following four to six hours. The extrarenal handling of potassium is affected by insulin, catecholamines, mineralocorticoids, acid-base status and extracellular osmolality.

Insulin

Cellular uptake of potassium by the muscle and the liver is facilitated by insulin. The mechanism by which insulin promotes cellular potassium uptake is not well established, although it appears to be independent of glucose uptake. Moore and co-workers [1] recently proposed that insulin stimulates the sodium-hydrogen exchange in muscle cells; this would increase intracellular sodium and pH, which in turn activates the sodium pump, increasing potassium uptake. The importance of insulin in regulating basal extracellular potassium concentration and the response to an acute potassium load is well established in studies by DeFronzo and associates[2] in which insulin secretion was inhibited by the use of somatostatin in normal controls and in patients with diabetes mel-

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litus. A rise in the basal serum potassium level of 0.6 mEq and decreased tolerance to potassium loads was found in normal subjects and in patients with type II diabetes mellitus. In contrast, serum potassium levels did not change in patients with type I diabetes mellitus (Figure 1). These changes are compatible with the results of suppression of insulin secretion in normal persons and in patients with type II diabetes mellitus; the lack of effect in patients with type I diabetes mellitus is consistent with the absence of endogenous insulin in these patients.

Catecholamines

D'Silva showed that an epinephrine injection produced transient hyperkalemia followed by sustained hypokalemia.[3] Recently DeFronzo and colleagues[4] reported that infusing a dose of epinephrine in humans to physiologic levels reduced the basal serum potassium level and increased the tolerance to a potassium load. Figure 2 shows that potassium chloride

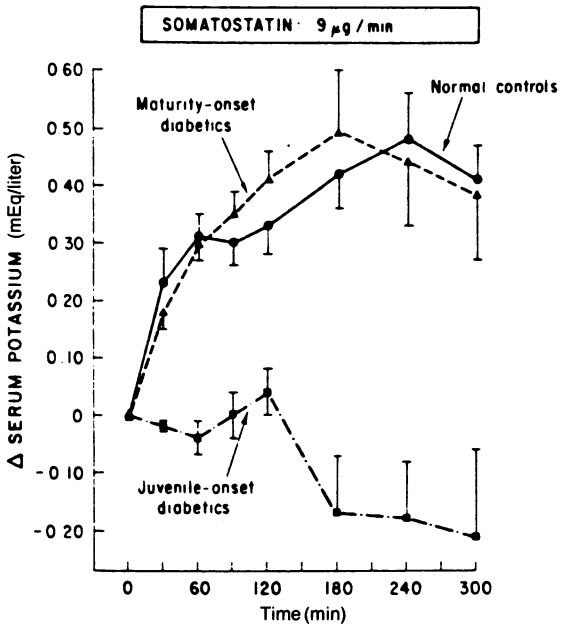

Figure 1.—The effect of somatostatin infusion on serum potassium concentration in normal controls (●), maturity-onset diabetics (▲) and juvenile-onset diabetics (■). (Reprinted with permission from DeFronzo et al.[2])

infusion (open circles) increased plasma potassium by 0.8 mEq per liter at 120 minutes. Pretreatment with epinephrine (open triangles) blunted the rise in plasma potassium during the potassium chloride infusion. The improvement in potassium tolerance was blocked by the simultaneous administration of propranolol hydrochloride (open squares), although propranolol alone had no significant effect on the plasma potassium level. The striking increase in plasma potassium during infusion of epinephrine plus propranolol presumably reflected the α-effects of infused epinephrine.[5] The hypokalemic effect of catecholamines has recently been reported to be mediated through a specific β_2-effect,[6] presumably because β_2-agonists directly stimulate the sodium pump. Propranolol and specific β_2-blockers blunt the hypokalemic response to exogenous epinephrine and also impair the uptake of potassium released from muscle during exercise, so that in patients treated with propranolol hyperkalemia may develop during exercise.[7]

Mineralocorticoids

The role of aldosterone in extrarenal potassium handling is controversial and difficult to assess because it primarily affects renal secretion of potassium. Aldosterone also stimulates potassium secretion by the colon, a factor that plays an important role in potassium regulation in hyperkalemic states associated with impaired renal excretion of potassium.

Acid-Base Status

Changes in acid-base state influence plasma potassium concentration independent of alterations of the external potassium balance.[8] In general acidosis increases potassium release from cells, and alkalosis stimulates potassium uptake by cells. The magnitude of the potassium shift depends on the nature, the severity and the chronicity of the acid-base disturbance. For example, hyperkalemia invariably occurs in metabolic acidosis produced by infusion of mineral acids such as hydrochloric acid or ammonium chloride. In contrast, if organic acids such as lactic acid are infused, only minimal changes in serum potassium are produced. In general, organic acids penetrate the cell more easily and may in fact enter the cell as the nondissociated acid so that no displacement of intracellular cations (potassium) occurs.[9,10] The exact mechanisms involved in potassium shifts during acid-base disturbances are not completely clear, although pH (such as proton concentration) appears to play a role. If serum pH decreases because of an increase in extracellular proton concentration, the gradient favors proton entry into the cell, and potassium might exit in exchange for protons. The reverse may occur during alkalosis. Changes in bicarbonate concentration without changes

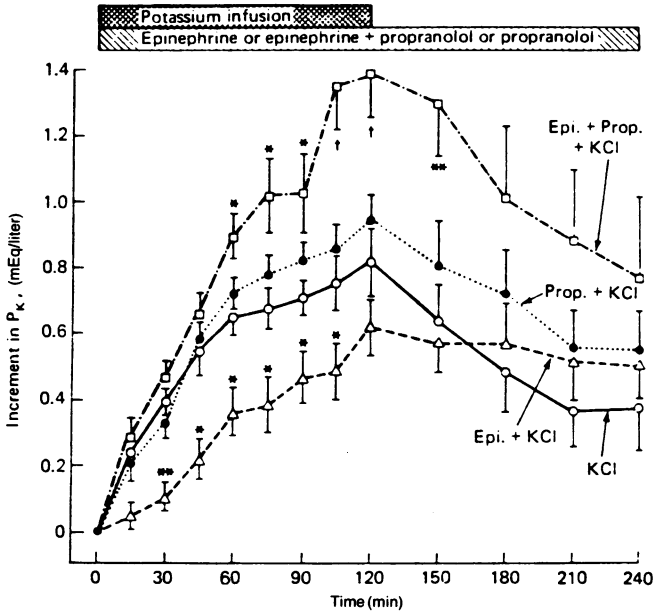

Figure 2.—Time course of change in plasma potassium concentration, following infusion of potassium chloride (○), epinephrine plus potassium chloride (△), epinephrine plus propranolol hydrochloride plus potassium chloride (□) and propranolol plus potassium chloride (●). Asterisk (*) denotes difference from the control values at .05 level of significance, and double asterisk (**) denotes differences at the .01 level of significance. (Reprinted with permission from DeFronzo et al.[4])

in pH also induce potassium shifts. An increase in extracellular bicarbonate concentration will induce potassium entry into cells and a fall in serum bicarbonate will favor the exit of potassium from cells.[11] In addition, intracellular pH may regulate the activity of the sodium pump; if intracellular acidosis inhibits the sodium pump, potassium uptake into the cells would be inhibited.

Extracellular Osmolality

Extracellular hypertonicity raises the serum potassium level. In anephric animals, hypertonic infusions produce a rise in serum potassium of 0.1 to 0.6 mEq per liter for each 10 mosm per kg of water increase in osmolality. This effect is independent of the nature of the solute producing the hypertonicity. The mechanisms responsible for this effect on extracellular potassium concentration may relate to active potassium chloride extrusion from the cells in response to intracellular hypertonicity.[12]

Regulation of Renal Potassium Excretion

The filtered load of potassium is about 700 mEq per day, 70% to 80% of which is reabsorbed by the proximal tubule and 10% of which is reabsorbed by the loop of Henle. The fraction of potassium reabsorbed in the proximal tubule and loop of Henle remains almost constant, despite 200-fold fluctuations (from 5 to 1,000 mEq) in urinary potassium excretion in response to changes in dietary potassium intake. The factors that regulate renal potassium excretion include diet, pH, distal delivery of flow and sodium and aldosterone.

Diet

The load of potassium in the diet regulates the capacity of the distal nephron to secrete potassium. Animals and humans exposed to a potassium-rich diet can handle a potassium load that would be lethal to animals receiving a normal or a low-potassium diet. This phenomenon is known as potassium adaptation and involves an increase in potassium uptake by nonrenal cells and enhanced potassium secretion by the distal tubule and collecting duct. Aldosterone seems to play a permissive role in potassium adaptation.

pH

Acidosis decreases potassium secretion and alkalosis increases potassium secretion by distal and collecting tubule cells. This may reflect changes in intracellular potassium activity, changes in basolateral and luminal permeability to potassium or changes in the activity of the sodium pump.

Distal Delivery of Flow and Sodium

One of the most important variables regulating renal potassium secretion is the rate of fluid and sodium delivery to the distal tubule.[13,14] Two factors might contribute to the accelerated rate of potassium secretion following enhanced distal delivery of fluid and sodium. As sodium reabsorption increases, an increase in transepithelial voltage (increasing luminal electronegativity) would favor potassium secretion. A second factor is the increase in flow rate, which decreases the luminal potassium concentration and maintains a chemical gradient that favors potassium secretion into the luminal fluid.

Aldosterone

Aldosterone stimulates sodium reabsorption and potassium secretion in the cortical collecting tubule.[15] The kaluretic effect of aldosterone depends on an adequate supply of sodium to the distal nephron. The stimulation of potassium secretion involves an increase in luminal permeability to sodium with an increase in luminal electronegativity, an increase in potassium permeability and a stimulation of the sodium pump.

TABLE 1.—*Causes of Hyperkalemia*

Increased Potassium Input
Through diet, salt substitutes
In hemolysis, gastrointestinal bleeding, crush injuries, catabolism
Decreased Renal Potassium Secretion
During inadequate distal delivery of sodium and fluid
Because of impaired renin-aldosterone axis
In Addison's disease, enzyme deficiencies, hypoaldosteronism, hyporeninism, from drugs (heparin, β-blockers, NSAIA, captopril)
From aldosterone antagonists (spironolactones, triamterene, amiloride)
In primary secretory defects
Sickle cell disease, systemic lupus erythematosus, after renal transplant, with obstructive uropathy, interstitial nephritis, congenital or familial primary secretory defects, amyloidosis
Abnormal Potassium Distribution
In acidosis, hypertonicity, from β-blockers, during periodic paralysis, succinylcholine, insulin deficiency, aldosterone deficiency, from exercise, tissue damage, digitalis

NSAIA = nonsteroidal anti-inflammatory agents

Etiology of Hyperkalemia

The major causative factors of hyperkalemia to be considered are increases in potassium input, redistribution of potassium between the intracellular and the extracellular compartments and impaired renal potassium excretion (Table 1).

Increased Potassium Input

Although increased potassium intake can cause hyperkalemia, this is extremely unusual unless an abnormality in internal potassium distribution or impaired renal excretion of potassium is present. Intravenous infusions containing potassium, salt substitutes, transfusions (bank blood 21 days old contains 30 mEq potassium per liter), hemolysis, gastrointestinal tract bleeding, crush injuries and cell catabolism all can raise serum potassium levels. Factitious hyperkalemia can be observed due to thrombocytosis or leukocytosis and is diagnosed by measuring the plasma potassium level.

Abnormal Potassium Distribution

Numerous conditions can affect the distribution of potassium between the intracellular and the extracellular spaces, including acidosis, extracellular hypertonicity, insulin deficiency, aldosterone deficiency, tissue damage, exercise, drugs such as digitalis that in toxic doses impair potassium uptake by the cells blocking the sodium pump, β-blockers that antagonize the action of β_2-agonists and succinylcholine, which depolarizes the cell membrane. Hyperkalemic periodic paralysis is a rare familial disorder characterized by hyperkalemia and a pronounced flaccid paralysis often precipitated by exercise or ingestion of small amounts of potassium (0.5 to 1 mEq per kg).

Decreased Renal Potassium Secretion

Defects in renal potassium handling occur in renal failure if impairment of the renin-aldosterone axis occurs, during therapy with "potassium-sparing" diuretics and in primary disorders of the distal nephron.

Acute renal failure is often accompanied by hyperkalemia, which may become life-threatening, especially in hypercatabolic patients. In cases of uncomplicated acute renal failure (such as in aminoglycoside nephrotoxicity), the serum potassium level should not increase by more than 0.5 mEq per day. In contrast, in chronic renal failure hyperkalemia is rarely a problem. Potassium excretion per nephron and by the colon is increased, and hyperkalemia only develops if dietary potassium is increased or oliguria supervenes. Exceptions are patients with chronic renal failure due to interstitial disease or diabetes mellitus, where hyperkalemia may become a problem if hypoaldosteronism is present.

Impairment of the renin-aldosterone axis occurs in Addison's disease, in selective hypoaldosteronism and in treatment with certain drugs. The lack of aldosterone in Addison's disease will impair renal potassium secretion. In addition, the volume contraction found in this condition will decrease distal sodium and fluid delivery. The destruction of the adrenal medulla decreases epinephrine release, which may contribute to the hyperkalemia by reducing potassium entry to muscle and liver cells.

Selective hypoaldosteronism is found mostly in elderly patients. Nearly all of these patients have low basal renin levels that do not normally increase if a patient is placed in an upright posture. This syndrome is often seen in diabetic patients or in patients with interstitial nephritis.[16] In 75% of the cases the hyperkalemia is asymptomatic and a hyperchloremic metabolic acidosis is present in 50% of the cases. The decreased renin levels have been attributed to a destruction of the juxtaglomerular apparatus by the underlying kidney disease. It is also possible that renin is suppressed by volume expansion due to primary salt retention. In some cases, the primary defect may be in aldosterone synthesis. A blunted secretory response of aldosterone to adrenocorticotropic hormone or angiotensin II infusions has been noted in some cases, and hyperkalemia resulting from the decrease in aldosterone levels would suppress the release of renin and thereby further suppress aldosterone secretion.[17,18]

Many drugs interfere with the function of the renin aldosterone axis at different levels; heparin may impair intrarenal synthesis of aldosterone, β-blockers decrease adrenergic stimuli to renin release, nonsteroidal anti-inflammatory drugs decrease prostaglandin synthesis and thereby inhibit renin release and converting enzyme inhibitors block the generation of angiotensin II from angiotensin I.

Potassium-sparing diuretics affect potassium handling in the collecting tubule. Spironolactone antagonizes the action of aldosterone in the collecting duct by competitive inhibition of aldosterone binding to the cytosolic receptor. Triamterene and amiloride hydrochloride block the luminal entry of sodium into the distal and collecting duct cells, decreasing the luminal electronegativity that normally favors potassium secretion and thereby causing hyperkalemia.

Decreased potassium clearance in the presence of normal aldosterone levels and resistance to exogenous mineralocorticoids has been reported in patients who have primary secretory defects. There are at least two different varieties of this syndrome. Classic pseudohypoaldosteronism is a congenital abnormality in children. The distal tubule is unresponsive to mineralocorticoids, and the syndrome is characterized by salt wasting, hyperkalemia and hyperchloremic acidosis. The syndrome usually corrects spontaneously by the age of 2 to 3 years. The other type of primary potassium secretory defect occurs without salt wasting and is often associated with interstitial kidney diseases.[19,20] This has been described in cases of sickle cell disease and lupus erythematosus and following renal transplantation. An unusual type is the inherited form of pseudohypoaldosteronism, which is characterized by hypertension and hyperkalemia with resistance to correction by exogenous mineralocorticoids.[21]

Clinical Features of Hyperkalemia

The changes induced by hyperkalemia are essentially confined to muscle weakness and abnormal cardiac conduction. A rise in serum potassium reduces the ratio of intracellular potassium concentration to the extracellular potassium concentration, resulting in a decrease in the resting membrane potential (depolarization) towards the excitation (threshold) level. As a consequence, depolarization is delayed, repolarization is accelerated and conduction velocity is slowed.[22,23] Muscular weakness and flaccid paralysis are rare manifestations of hyperkalemia.

The most important effects of hyperkalemia are related to changes in electrophysiologic properties of the heart. The specialized conduction tissue and the atrial and ventricular muscle fibers are affected. The electrocardiogram often reflects these changes. The plasma potassium concentration at which electrocardiographic changes are seen varies, depends on how rapidly the serum potassium level rises and is potentiated by the presence of hypocalcemia. Hyponatremia and acidosis also potentiate the adverse effects of hyperkalemia on the heart.

The earliest electrocardiographic changes are usually narrowing and increased amplitude of the T waves. The QT interval often shortens and as levels of serum potassium increase (generally to over 6.5 mEq per liter), widening of the QRS complex occurs. With serum potassium levels greater that 7 mEq per liter, P waves progressively flatten and broaden and the PR interval increases. At plasma potassium of 8 to 9 mEq per liter, the P waves disappear, and ST changes that suggest ischemic injury or pericarditis may occur. At this point, asystole or ventricular fibrillation is imminent.

Because progression to fatal cardiotoxic reaction is unpredictable, treatment should be instituted without delay if the serum potassium level is above 6.5 mEq per liter even if the results of an electrocardiogram are normal.

Treatment of Acute Hyperkalemia

Immediate treatment should be initiated if an abrupt rise in the serum potassium level to 6.5 mEq per liter or more occurs or if any degree of hyperkalemia associated with electrocardiographic changes is present. Treatment of an acute state includes maneuvers to immediately counteract the effects of potassium at the membrane level, to shift potassium into the cells and to remove potassium from the body.[22,23]

Calcium will increase the threshold potential, reestablishing the difference between the threshold and the resting potential. This approach directly antagonizes the effects of hyperkalemia at the membrane level. A dose of 10 to 30 ml of calcium gluconate (10%) should be administered intrave-

nously over three to five minutes with continuous electrocardiographic monitoring. A second dose may be required. The effect is immediate but only lasts for 30 to 60 minutes. If the patient is receiving digitalis, calcium could be hazardous because the action of digitalis is potentiated

In patients with hyponatremia and hypovolemia, a beneficial effect of sodium chloride has been reported beyond the dilutional effect of volume expansion on hyperkalemia. Sodium may antagonize the effects of potassium on cell membranes. More commonly than sodium chloride, hypertonic sodium bicarbonate is given intravenously (50 to 100 ml of a 7.5% solution). Both the sodium and bicarbonate favor potassium entry to cells.

Atrioventricular block or severe bradycardia that is not reversed in minutes by the above measures is an indication for insertion of a transvenous pacemaker.

Even in the absence of acidosis, bicarbonate will shift potassium into cells. Bicarbonate will also stimulate potassium secretion by the distal tubule by increasing distal sodium delivery and by delivering a relatively impermeant anion to the distal tubule. Sodium bicarbonate infused over a period of five to ten minutes is recommended. The hypokalemic effect starts at five to ten minutes and lasts for two hours. If no effect is seen in 15 minutes, a second bolus can be infused. Secondary effects of sodium bicarbonate infusion include volume overload, seizures due to decreased ionized calcium and increased serum osmolality. Insulin increases potassium uptake by muscle and liver cells. This effect is independent from glucose entry into the cells, but glucose must be administered simultaneously to prevent hypoglycemia; 500 ml of 10% dextrose glucose plus 10 units of insulin infused over one hour is recommended. The onset of the effect is 30 minutes and lasts for four to six hours. The potassium level will decrease by 0.5 to 1.2 mEq per liter in one to two hours.

The above measures will only transiently decrease the serum potassium concentration. More definitive treatment requires elimination of potassium from the body, which can be accomplished by stimulating renal excretion of potassium or by the use of cation exchange resins or dialysis. If renal function is present, administration of saline or sodium bicarbonate is recommended to stimulate potassium secretion by the distal and collecting tubule. Increased distal delivery of sodium can be facilitated by the concomitant use of loop diuretics like furosemide. Sodium polystyrene sulfonate (Kayexelate) will decrease serum potassium by exchanging potassium for sodium in the gastrointestinal tract. Each gram of Kayexelate will remove 0.5 to 1 mEq of potassium in exchange for 2 to 3 mEq sodium. Sodium polystyrene also removes calcium and magnesium and can be administered orally (25 grams per dose) or by a retention enema (50 grams per dose) four to six times a day. Sorbitol should be administered simultaneously to induce diarrhea. The effect begins at one to two hours, and, on average, 50 grams of Kayexelate will lower the serum potassium level by 0.5 to 1 mEq per liter. If these measures are ineffective, or if renal failure is present, hemodialysis and peritoneal dialysis are effective in removing potassium from the body. Potassium clearance with hemodialysis is higher than with peritoneal dialysis. Hemodialysis can remove about 40 mEq of potassium from a hyperkalemic patient in the first hour, whereas peritoneal dialysis will remove between 180 and 240 mEq in 36 to 48 hours.

Treatment of Chronic Hyperkalemia

Chronic hyperkalemia is usually due to decreased secretion of potassium by the kidney. The treatment depends on the specific cause of hyperkalemia. In general, dietary potassium restriction to 40 to 60 mEq per day is recommended. Treatment of acidosis and hypovolemia, if present, will ameliorate the magnitude of the hyperkalemia. Avoidance of drugs that increase serum potassium concentration is recommended, including potassium-sparing diuretics, prostaglandin inhibitors, heparin, β-blockers and angiotensin-converting enzyme inhibitors. If selective hypoaldosteronism is present, mineralocorticoids are the treatment of choice, and large doses are usually required. If Addison's disease is the cause of the hyperkalemia, glucocorticoids and dietary sodium supplementation usually are sufficient but in some patients mineralocorticoid replacement is required. When a distal tubular secretory defect is present, hyperkalemia is in general difficult to treat, but many of these patients respond to thiazides or loop agents. Hyperkalemia due to hyperkalemic periodic paralysis may respond to thiazides. A β_2-agonist (albuterol) has recently been used to treat this condition.[24]

In conclusion, the management of hyperkalemia requires an exact definition of underlying pathophysiology. The acute response to potassium loads and consequently the immediate forms of therapy are directed towards the extrarenal homeostatic mechanisms. Regardless of the cause of hyperkalemia, immediate therapy can be instituted as the diagnostic workup is initiated. Chronic hyperkalemia usually denotes a defect in renal potassium secretion that may respond to maneuvers which increase delivery of sodium to the distal tubule and enhance sodium reabsorption at that site. If renal failure is present, then potassium removal via the gastrointestinal tract or dialysis is required, in addition to careful monitoring of dietary potassium intake.

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